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Attorney Docket 040750-5001-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: **Huang et al.**

Application No. **09/071,541**

Filed: **May 4, 1998**

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Group Art Unit: **1623**

Examiner: **K. Fonda**

For: **Methods to Modulate the Resistance of Cells to Apoptosis Mediated by Mutant Epidermal Growth Factor Receptors**

APPELLANTS' BRIEF UNDER 37 C.F.R. 1.192

This brief is in furtherance of the Notice of Appeal, filed in this application on April 28, 2003. The fees required under 37 C.F.R. 1.17(f) are being filed concurrently herewith. The period for filing this brief has been extended through November 28, 2003 by the accompanying petition for a four month extension of time and payment of the appropriate fee. This brief is transmitted in triplicate.

1. The Real Party in Interest

The real parties in interest in this appeal is the Ludwig Institute for Cancer Research and the Yisum Research Development Company of the Hebrew University of Jerusalem.

2. Related Appeals and Interferences

None.

3. Status of Claims in Application

Claims 1 to 16 are pending in the application. No claims have been allowed. Claims 1 to 16 have been finally rejected and are on appeal. Claims 1 to 16 have been rejected under 35 U.S.C. 103(a).

4. Status of Amendments

An amendment under 37 C.F.R. 1.116 was filed after the final Office Action dated November 26, 2002 (Paper No. 24) along with a declaration under 37 C.F.R. 1.132 by Dr. Webster Cavaneer, a designated inventor of the present application. This amendment was entered

and rejections under 35 U.S.C. 102 and 112 were withdrawn while the rejection under 35 U.S.C. 103(a) was maintained in an Advisory Action dated July 3, 2003.

5. Summary of Invention

Appellant's invention relates to compositions and methods for modulating an apoptosis-inhibiting effect in a target cell or tissue of a mutant Epidermal Growth Factor Receptor (Δ EGFR) gene. The composition comprises a mixture of an agent effective to induce apoptosis with an amount of a tyrosine kinase inhibitor that is effective to reduce resistance to induction of apoptosis in a target cell in tissue expressing a Δ EGFR gene. The method of modulating an apoptosis-inhibiting effect of a Δ EGFR gene comprises administering to the target cell or tissue an amount of tyrosine kinase inhibitor effective to reduce resistance to induction of apoptosis in combination with a therapy effective to induce apoptosis.

6. Issues on Appeal

Does Han *et al.* (Cancer Research (1996) 56, 3859-3861) in view of Reed *et al.* (U.S. Patent 5,831,066) and in further in view of Tsai *et al.* (Cancer Research (1996) 56, 1068-1074) establish a *prima facie* case of obviousness under 35 U.S.C. 103(a).

7. Groupings of Claims

Claims 1 to 8 relate to the methods of the invention, claims 9 to 12 relate to the compositions of the invention, and claims 13 to 16 relate to a kit comprising the compositions of the invention.

8. Arguments

Claims 1 to 16 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Han *et al.* (Cancer Research (1996) 56, 3859-3861) in view of Reed *et al.* (U.S. Patent 5,831,066) and in further in view of Tsai *et al.* (Cancer Research (1996) 56, 1068-1074). Failing to establish a *prima facie* case of obviousness, this rejection is improper and should be reversed.

a. Statement of the Rejection

In the final Office Action dated November 26, 2002 the Han *et al.* reference was cited as teaching that tyrphostin AG1478 is a tyrosine kinase inhibitor that preferentially inhibits human glioma cells expressing the mutant Δ EGFR rather than a wild-type EGFR. The Examiner states that this reference also suggests tyrphostin AG1478 may be therapeutically useful with regard to glioblastomas, breast, lung and ovarian cancers because the Δ EGFR mutation occurs frequently in these cancers and tyrphostin AG1478 is a relatively specific inhibitor of Δ EGFR. The Examiner relies upon the Reed *et al.* reference for teaching that cisplatin, taxol (also known as paclitaxel) and vincristine are known cancer chemotherapeutic agents which have in common an ability to induce apoptosis in cancer cells. Lastly, the Examiner relies on the Tsai *et al.* reference as teaching that tyrphostin AG825 is a selective tyrosine kinase inhibitor able to enhance the sensitivity of certain cancer cells to the chemotherapeutic agents doxorubicin, etoposide and cisplatin.

The Examiner concluded that the ordinary artisan would have been motivated to combine the Han *et al.* reference (*i.e.*, to use the selective tyrosine kinase inhibitor tyrphostin AG1478 for treatment of glioblastomas, breast, lung and ovarian cancers), with the teachings in the Tsai *et al.* (*i.e.*, AG825 was also a selective tyrosine kinase inhibitor) and Reed *et al.* (*i.e.*, cisplatin, taxol, and vincristine were chemotherapeutic agents known to induce apoptosis in cancer cells) references, to reach the expectation that the claimed combination therapy would result in modulation of the apoptosis-inhibition effect of Δ EGFR. The Examiner also stated that the skilled worker would be motivated to combine the elements of the claimed pharmaceutical composition or kit for treating cancer because it would enhance compliance with an appropriate treatment regimen and provide convenience for both clinician and patient.

The Examiner also asserted that it would have been obvious to combine a tyrosine kinase inhibitor (such as Tyrophostin AG1478), in combination with a therapy that is effective to induce apoptosis, or to increase the rate of apoptosis, in the cell or tissue (such as cisplatin, paclitaxel or vincristine) “to obtain the expected combination of therapeutic benefits with regard to cancer treatment” (see Office Action dated December 14, 2001 at page 5). The Examiner then asserts that “an ordinary skilled worker would have expected the claimed combination therapy to result in modulation of the apoptosis-inhibiting effect of Δ EGFR” (see Office Action dated December 14, 2001 at page 5).

b. Response to the Rejection

i. The cited references do not contain any motivation to combine their respective teachings.

Appellants submit that the Examiner has failed to identify the requisite motivation from the prior art to combine the claimed classes of compounds. In order to establish a *prima facie* case of obviousness, the prior art itself must: (1) suggest to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process, and (2) reveal that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988); *In re Dow Chemical*, 837 F.2d 469, 473 (Fed. Cir. 1989). Appellants' invention is predicated on the discovery that the expression of mutant EGFR genes (Δ EGFR) in cancer cells can suppress the apoptosis inducing activity of chemotherapeutic agents (see page 8, lines 26-28 of the specification). Without such a discovery, Appellants respectfully submit that there would be no motivation to combine the claimed classes of agents.

In combining the cited references, the Examiner states that "the ordinary skilled worker would have been motivated to do so [combine the teachings of the cited references] to obtain the expected combination of therapeutic benefits with regard to cancer treatment" (see Office Action dated December 14, 2001 at page 5). None of the cited references suggests that a tyrosine kinase inhibitor such as Tyrophostin AG1478 could be used in combination with the claimed class of apoptosis inducing drugs (*e.g.*, chemotherapeutic agents).

The Han *et al.* reference does not even use or disclose the word "apoptosis" anywhere in the publication. The Reed *et al.* reference does not address the use of tyrosine kinase inhibitors for any purpose. The Examiner states that the disclosure by Tsai *et al.* of the ability of selective tyrosine kinase inhibitors to enhance the sensitivity of certain chemotherapeutic cancer agents would be sufficient motivation for the skilled artisan to expect the combination of these agents to modulate the apoptosis-inhibiting effect of the mutant EGFR gene (see Office Action dated November 26, 2002 at page 4). Appellants disagree because given the broad number of chemotherapeutic agents with distinct mechanisms of action, the skilled artisan at the time of the invention would not have been motivated or even had an expectation of success with regard to the claimed method directed to the combination of two specific classes of compounds (*i.e.*, a tyrosine kinase inhibitor with the claimed properties and a second agent which induces apoptosis or the

rate of apoptosis). Chemotherapeutic agents fall in many different drug categories with multiple and distinct mechanisms of action. Even given the disclosure of Tsai *et al.*, the skilled artisan would not have expected a single class of compounds (*i.e.*, tyrosine kinase inhibitors) to be effective in combination with all chemotherapeutic agents let alone the specific class of agents recited in the claims.

To remedy these lack of teachings in the cited references, the Examiner improperly relies on the teachings of the specification. For instance, the Office Action asserts that “an ordinary skilled worker would have expected the claimed combination therapy to result in modulation of the apoptosis-inhibiting effect of Δ EGFR” (see Office Action dated December 14, 2001 at page 5). As discussed above, none of the cited references disclose that Δ EGFR is even involved in the modulation of the apoptosis in a tumor cell and this discovery can be found only in the instant application. Respectfully, reliance on this motivation to combine the references is improper.

ii. All of the claim limitations are not taught in the cited references.

The Examiner’s rejection is improper because all of the claim limitations are not disclosed in the cited references. As the Examiner acknowledges, the Han *et al.* reference does not teach the use of tyrosine kinase inhibitors in combination with apoptosis inducing factors (see Office Action dated December 14, 2001 at page 4). In fact, the Han *et al.* reference is silent with regard to any effects of tyrosine kinase inhibitors on apoptosis. The Reed *et al.* reference does not remedy the deficiencies of the Han *et al.* reference since it does not address the use of tyrosine kinase inhibitors for any purpose. A word search of the text of the specification of the Reed *et al.* reference indicates that it contains neither the word “tyrosine” nor the word “kinase” alone or in combination. Clearly, the Reed *et al.* reference does not teach the use of tyrosine kinase inhibitors to modulate apoptosis.

The Tsai *et al.* reference on which the Examiner relies for motivation teaches that certain tyrosine kinase inhibitors enhance the sensitivity of certain cancer cells to chemotherapeutic agents. This reference does not address the modulation of apoptosis in cells or tissues having mutant EGFR genes. Since there is no teaching in either reference with regard to an effective amount of a tyrosine kinase inhibitor to modulate resistance to apoptosis mediated by a Δ EGFR, the cited references do not teach all the limitations of the present claims.

iii. The Examiner has improperly relied upon inherency in a rejection under 35 U.S.C. 103.

The Examiner has improperly relied on inherency to support the instant rejection. The Examiner contends that it is not necessary that any of the cited references disclose that a ΔEGFR gene is involved in modulation of apoptosis in a tumor cell. The pending claims are drawn to methods, compositions and kits relating to the use of a tyrosine kinase inhibitor to reduce the inhibition to apoptosis associated with certain therapies. The nature of the inhibition of apoptosis and the relevant embodiments of the invention are more particularly set forth in the claims. It has been acknowledged that the foregoing is not disclosed in the art (see Office Action dated June 23, 1999 at page 5). Yet, in rejecting the claims for obviousness, it was stated:

if tyrphostin AG1478 [as disclosed in Han] is a relatively specific inhibitor of human glioma cells expressing ΔEGFR, and is useful for treating cancer, then it must ‘modulate an apoptosis-inhibiting effect’ as recited in instant claim 1. Han need not have used these words, and need not have even understood the mechanism as Applicant does. It is sufficient that Han’s teaching, when taken in view of the teaching of Reed, would have suggested to the ordinarily skilled worker to do what Applicant has done

(see Office Action dated February 17, 2000 at page 5). Clearly, Han *et al.* does not explicitly state or suggest that the use of AG1478 will reduce the inhibition to apoptosis that has been found, for example, with conventional therapies such as cisplatin. Appellants respectfully submit, however, that these inherent properties of AG1478, properties first disclosed by Appellants in the pending application, were incorrectly considered by the Examiner to reject the pending claims as obvious.

It is long and well established that “inherency” and “obviousness” are distinct concepts, which must not to be confused. See *e.g.*, *W.L. Gore & Associates v. Garlock Inc.*, 721 F.2d 1540, 1555 (Fed. Cir. 1983). Appellants submit that the issue is not what may or may not be inherent in the cited references, but rather what is known to the ordinary, skilled artisan from those references. As stated in *In re Newell*, 891 F.2d 899, 901 (Fed. Cir. 1989), “that which may be inherent is not necessarily known ... obviousness cannot be predicated on what is unknown” (Id. at 901); see also *In re Rijckaert*, 9 F.3d 1531, 1535 (Fed. Cir. 1993); *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 1576 (Fed. Cir. 1986) (holding claims not invalid where defendant

failed to show that “inherency would have been obvious to those skilled in the art when invention ... was made”).

Applied here, the foregoing authorities make it clear that the inherent and unknown properties of AG1478 in conjunction with other therapies or agents cannot form the basis of an obviousness rejection. Because the art is devoid of any suggestion that the use of AG1478 would (or even might) reduce the recited resistance to apoptosis associated with a therapy or an agent, the Examiner’s rejection is improper and should be withdrawn.

iv. The prior art teaches away from the claimed invention.

The Examiner’s rejection is improper and should be withdrawn because of the non-obviousness of Appellants’ invention is further supported by the contrary teachings of the prior art (MPEP 2145). Specifically, U.S. Patent 5,597,798 (Howell *et al.*) discloses that the administration of EGF increases sensitivity to agents such as cisplatin. EGF is commonly known to increase the tyrosine kinase activity of the EGF receptor (EGFR). Yet, Appellants achieve greater cell sensitivity to agents not by increasing kinase activity, but by reducing it with inhibitors. Had Appellants or the artisan of ordinary skill followed the teachings of Howell *et al.*, they would never have discovered that tyrosine kinase inhibitors can play a critical role in combination cancer chemotherapies that induce apoptosis with tyrosine kinase inhibitors.

In response to Appellants’ arguments, the Examiner states that Howell *et al.* is taken out of context (see Office Action dated June 6, 2001 at page 7). The Examiner cites Guilli *et al.* (Cell Growth Differ. 7, 173-178) as being representative of the context of the entire state of the prior art. Guilli *et al.* teaches that a higher dose of EGF inhibited cell proliferation while a lower dose increased cell proliferation but does not disclose any experimental data involving chemotherapeutic agents. Guilli *et al.* therefore cannot be compared with the teachings of Howell *et al.* because this reference did not measure the effect of tyrosine kinase inhibitors on the activity of chemotherapeutic agents. The Examiner has therefore incorrectly characterized the state of the prior art in her responding to Appellants’ arguments that the prior art teaches away from the claimed invention.

v. The unexpected synergistic properties of the invention are not suggested by the cited references.

Assuming *arguendo* that the Examiner is found to have set forth a *prima facie* case of obviousness, Appellants have provided adequate evidence as set forth in the instant application, that the claimed subject matter of claims 1 to 16 yields unexpectedly superior synergistic results. In response to the Appellants' arguments related to synerism, the Examiner has stated that it is well established that combining known compounds with known characteristics is not patentable "where the results obtained thereby are no more than the additive effects of the ingredients" (citation omitted). Appellants respectfully submit that this statement is not applicable to the present facts since the results obtained by the claimed combination is greater than the sum of the results obtained by the individual ingredients. In view of this, Appellants respectfully request reconsideration and withdrawal of the present rejection.

Appellants respectfully draw the Board's attention to Figure 6B. The y axis is a measure of the percentage of cells that are apoptotic as determined by TUNEL assays. The x axis describes the various treatments applied to the cells, these treatments involved combinations of cisplatin and a specified concentration (μM) of one of the following tyrophostins: AG1478, AG1517, AG1479, or AG1536. The (+) and (-) is an indication of the presence or absence of cisplatin (CDDP) respectively. The solid dark bars indicate the percentage of apoptotic cells in the presence of cisplatin while the open bars indicate the percentage of apoptotic cells in the absence of cisplatin. Thus, the open bar is the percentage of apoptotic cells that result from the presence of the tyrosine kinase inhibitor at the indicated concentration.

Appellants respectfully point out that when cisplatin is applied without AG1478 (first dark bar from the left) the percentage of apoptotic cells is less than ten percent or approximately eight percent. Application of 10 μM of AG1478 without cisplatin provides a barely discernable apoptotic response. Summing the percentage of apoptotic cells expected to result from the combination of cisplatin and 10 μM AG1478 would predict ten percent or less of the cells to be apoptotic. Unexpectedly, the actual percentage of cells that are apoptotic as a result of this treatment is approximately seventeen percent or nearly double the expected amount. Treatments of 15 and 20 μM AG1478 without cisplatin result in approximately two percent and four percent apoptotic cells respectively (third and fourth open bars from the left). When these amounts are added to the approximately eight percent apoptotic cells caused by cisplatin alone, the expected

percentage of apoptotic cells would be approximately ten percent and twelve percent, respectively if the results were merely additive. Once again the observed percentage of apoptotic cells is unexpectedly high. The combination of 15 μ M AG1478 and cisplatin results in approximately twenty-four percent apoptotic cells, more than double the expected value, while the combination of 20 μ M AG1478 and cisplatin results in approximately twenty-five percent apoptotic cells, once again more than double the expected value. These results clearly indicate that the presently claimed methods and compositions have unexpected, superior properties compared to the prior art.

Respectfully, on these results alone, the instant claims should be allowed over the cited prior art. See MPEP 716.02(a); *Merck and Company v. Biocraft Laboratories Inc.*, 874 F.2d 804 (Fed. Cir. 1989); *Ex Parte Nutrasweet Company*, 19 USPQ2d 1586 (Bd. Pat. App. Inter. 1991). The Examiner has previously acknowledged that the results are not merely additive (see Office Action dated December 14, 2001 at page 7). The Examiner also indicated that the amounts taught or suggested by the references are those which would meet the claim limitations (see Office Action dated December 14, 2001 at page 6). Appellants amended claims 1, 3 & 9 to provide the feature that the kinase inhibitor be present in a synergistically effective amount. In response, the Examiner rejected the amendment as encompassing new matter under 35, U.S.C. 112 (first paragraph). Appellants do not agree with the Examiner's rejection but have nonetheless removed this language from the claims to put them in better condition for appeal. The absence of the term "synergistically" from the pending claims, however, does not preclude consideration of the unexpected superior effects demonstrated by the claimed combination of agents in relation to the instant rejection.

c. Summary of Argument

Appellants respectfully submit that the Examiner has failed to provide the requisite motivation from the prior art to combine the claimed classes of compounds, has relied upon the teachings in the specification as motivation to combine the cited references, has improperly relied on inherency principles in an obvious rejection and has ignored the significance of the unexpected results set forth in the instant application. For these reasons, a *prima facie* case of obviousness has not been set forth and Appellants have provided sufficient evidence of unexpected results to rebut any arguments of obviousness.

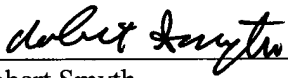
d. Conclusion

As shown by the preceding arguments, claims 1 to 16 are patentable under 35 U.S.C. 103 in view of the cited references. Appellants respectfully request reversal of the rejections under 35 U.S.C. 103 and allowance of pending claims 1 to 16.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. 1.136(a)(3).

Dated: **November 26, 2003**
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Appendix A

Claims On Appeal

1. (Five times amended) A method of modulating an apoptosis-inhibiting effect in a target cell or tissue of a mutant EGFR gene, comprising administering to the cell or tissue an amount of a tyrosine kinase inhibitor that is effective to reduce resistance to induction of apoptosis or resistance to an increased rate of apoptosis in the target cell or tissue in combination with a therapy that is effective to induce apoptosis or to increase the rate of apoptosis in the cell or tissue.
2. The method of claim 1, wherein the mutant EGFR gene is constitutively active.
3. The method of claim 2, wherein the mutant EGFR gene is Δ EGFR.
4. The method of any of claims 1 to 3, wherein the cell or tissue is a tumor selected from the group consisting of glioma, breast cancer, lung cancer and ovarian cancer.
5. The method of claim 4, wherein the tumor is a glioma.
6. The method of claim 1, wherein the apoptosis inducing or apoptosis rate increasing therapy is the administration of an agent selected from the group consisting of cisplatin, paclitaxel and vincristine.
7. The method of claim 1, wherein the tyrosine kinase inhibitor is relatively selective for a tumor specific mutant EGFR.
8. The method of claim 1, wherein the tyrosine kinase inhibitor is selected from the group consisting of Tyrphostin AG1478 and its derivatives.
9. (Four times amended) A pharmaceutical composition comprising a mixture of:

(A) an amount of an agent that is effective to induce apoptosis or to increase a rate of apoptosis in a target cell or tissue; and

(B) an amount of a tyrosine kinase inhibitor that is effective to reduce resistance to induction of apoptosis or resistance to the increased rate of apoptosis in the target cell or tissue expressing a mutant EGFR gene, the resistance being mediated by a mutant EGFR.

10. The composition of claim 9, wherein the apoptosis inducing or apoptosis rate increasing agent is an antitumor agent selected from the group consisting of cisplatin, paclitaxel and vincristine.

11. The composition of claim 9, wherein the tyrosine kinase inhibitor is relatively selective for a tumor specific EGFR.

13. (Four times amended) A kit for treating cancer comprising:

(A) an amount of an agent that is effective to induce apoptosis or increase a rate of apoptosis in a target cell or tissue; and

(B) an amount of a tyrosine kinase inhibitor that is effective to reduce resistance to induction of apoptosis or resistance to the increased rate of apoptosis in the target cell or tissue expressing a mutant EGFR gene, the resistance being mediated by a mutant EGFR.

14. The kit of claim 13, wherein the apoptosis inducing or apoptosis rate increasing agent is an antitumor agent selected from the group consisting of cisplatin, paclitaxel and vincristine.

15. The kit of claim 13, wherein the tyrosine kinase inhibitor is relatively selective for a tumor specific EGFR.

16. The kit of claim 13, wherein the tyrosine kinase inhibitor is selected from the group consisting of Tyrphostin AG1478 and its derivatives.